

HLA-E-expressing pluripotent stem cells escape allogeneic responses and lysis by NK cells.

Journal: Nat Biotechnol

Publication Year: 2017

Authors: German G Gornalusse, Roli K Hirata, Sarah E Funk, Laura Riobos, Vanda S Lopes, Gabriel Manske, Donna Prunkard, Aric G Colunga, Laila-Aicha Hanafi, Dennis O Clegg, Cameron Turtle, David W Russell

PubMed link: 28504668

Funding Grants: Stem cell based treatment strategy for Age-related Macular Degeneration (AMD), Stem cell based treatment strategy for Age-related Macular Degeneration (AMD), Phase 1 Safety Assessment of CPCB-RPE1, hESC-derived RPE Cell Coated Parylene Membrane Implants, in Patients with Advanced Dry Age Related Macular Degeneration

Public Summary:

In efforts to create a universal stem cell line, an HLA-class II negative cell line, HLA-E-Expressing Pluripotent Stem cell (PSC) line, was derived by disrupting the beta-2 microglobulin (B2M) gene in human embryonic stem cells (hESC). Forced expression of minimally polymorphic HLA-E molecules is carried out as such cells are also vulnerable to lysis by natural killer (NK) cells. These HLA-engineered PSCs and their differentiated derivatives can be used as universal donors as they lack HLA class II expression which drive immune-mediated rejection. Thus universal stem-cells would address immune rejection responses that may be elicited in both iPSC and the hESC.

Scientific Abstract:

Polymorphisms in the human leukocyte antigen (HLA) class I genes can cause the rejection of pluripotent stem cell (PSC)-derived products in allogeneic recipients. Disruption of the Beta-2 Microglobulin (B2M) gene eliminates surface expression of all class I molecules, but leaves the cells vulnerable to lysis by natural killer (NK) cells. Here we show that this 'missing-self' response can be prevented by forced expression of minimally polymorphic HLA-E molecules. We use adeno-associated virus (AAV)-mediated gene editing to knock in HLA-E genes at the B2M locus in human PSCs in a manner that confers inducible, regulated, surface expression of HLA-E single-chain dimers (fused to B2M) or trimers (fused to B2M and a peptide antigen), without surface expression of HLA-A, B or C. These HLA-engineered PSCs and their differentiated derivatives are not recognized as allogeneic by CD8⁺ T cells, do not bind anti-HLA antibodies and are resistant to NK-mediated lysis. Our approach provides a potential source of universal donor cells for applications where the differentiated derivatives lack HLA class II expression.

Source URL: <https://www.cirm.ca.gov/about-cirm/publications/hla-e-expressing-pluripotent-stem-cells-escape-allogeneic-responses-and>